

PATENT SPECIFICATION

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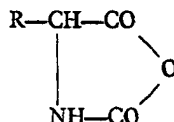


(54) PROCESS FOR THE POLYMERIZATION OF α -AMINO ACID-N-CARBOXY ANHYDRIDES

(71) We, KYOWA HAKKO KOGYO, Co. LTD., a corporation organised under the laws of Japan, of 4 Ohtemachi-1-chome, Chiyoda-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly

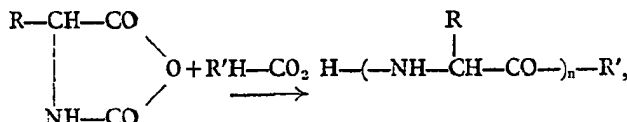
described in and by the following statement:—

This invention relates to a process for the polymerization of α -amino acid-N-carboxy anhydrides. More particularly, it relates to a process for polymerizing N-carboxy anhydrides of α -amino acids having the general formula



wherein R is an organic residue. Even more particularly, the invention relates to the polymerization of said N-carboxy anhydrides using imidazole derivatives. Hereinafter, for the sake of convenience, α -amino acid-N-carboxy anhydrides will be referred to as NCA.

It is generally known in the art that NCA polymerize with the release of carbon dioxide in the presence of amines, or sodium alcoholates for example as indicated by the following reaction scheme:



wherein R has the same meaning as indicated above and R' is a hydroxyl or alkoxyl group. However, the use of even more efficient initiators for this reaction would be highly desirable.

Accordingly, one of the objects of the present invention is to provide an improved process for polymerizing α -amino acid-N-carboxy anhydrides which overcomes the disadvantages and deficiencies of the prior art methods.

Another object of the present invention is to provide a process for the polymerization

of α -amino acid-N-carboxy anhydrides which may be carried out in an efficacious manner.

A further object of the invention is to provide a novel polymerization initiator for α -amino acid-N-carboxy anhydrides and derivatives thereof.

A still further object of the invention is to provide the polymerization products resulting from the polymerization of α -amino acid-N-carboxy anhydrides.

As the result of various studies and experiments on the polymerization of NCA, the present inventors have found that

imidazole compounds, which have not been used as polymerization initiators heretofore, bring about a remarkable effect when used as polymerization initiators for α -amino acid-N-carboxy anhydrides.

The imidazole compounds used in the present invention exhibit a polymerization-initiating ability which is equal to or even superior to that of the conventionally used organic bases or sodium alcoholates. Furthermore, a majority of these compounds exist in the form of crystals, so that they can be handled and stored easily, as compared with the organic bases which tend to contain water which substantially reduces the polymerization-initiating ability, and with sodium alcoholate which is readily decomposed in the presence of water.

In the present invention, the α -amino acid-N-carboxy anhydrides used are any of the NCA which can be synthesized from the corresponding α -amino acids, i.e., neutral amino acid, acidic amino acid monoesters and N-substituted derivatives of basic amino acids and derivatives thereof. Examples thereof are glycine, alanine, α -aminobutyric acid, valine, norvaline, leucine, isoleucine, norleucine, phenylalanine, O-substituted serine, O-substituted homoserine, O-substituted threonine, S-substituted cysteine, cystine, methionine, aspartic acid- β -monoester, glutamic acid- γ -monoester, α -aminoadipic acid- δ -monoester, proline, N²-substituted ornithine and N²-substituted lysine. These amino acids and amino acid derivatives may be either optically active or inactive.

The polyamino acids obtained by polymerising N-carboxy anhydrides of amino acids or amino acid derivatives such as those enumerated hereinabove, using the polymerization initiators of the present invention, find various applications as fibers, films, synthetic leathers and as additives for foodstuffs. The resultant polyamino acids have a particularly high degree of polymerisation and are therefore excellent not only in their ability to form films, but also in their fiber-forming properties. This is why the polyamino acids can be readily used in a wide range of applications including the production of synthetic fibers and artificial leathers.

Imidazole compounds which may be used as polymerisation initiators in accordance with the present invention are the following:—

1. Imidazole derivatives

a) Aryl-, aralkyl-, alkaryl- and alkyl imidazole derivatives. Among these are imidazole, 1-phenyl-imidazole, 1-methylimidazole, 1-benzylimidazole, 2-methylimidazole, 2-phenylimidazole, 4-methylimidazole, 4-phenylimidazole, 1,2-dimethylimidazole, 1,4-dimethylimidazole, 1,

5-dimethylimidazole, 1-ethyl-2-methyl-imidazole, 4,5-diphenylimidazole and 2,4,5-trimethylimidazole.

b) Halogen, haloalkyl and hydroxyalkyl derivatives. Among these are 2-bromoimidazole, 2-bromo-4-methylimidazole, 5-chloro-1-methylimidazole, 4-chloromethylimidazole, 5-chloromethyl-1-methylimidazole, 5-hydroxymethylimidazole, and 5-hydroxymethyl-1-methylimidazole.

c) Nitro, amino, and aminoalkyl derivatives. Among these are 4(5)-nitroimidazole, 5(4)-methyl-4(5)-aminoimidazole, 2-aminoimidazole, 4(5)-aminoimidazole, and 4(5)-methyl-5(4)-nitroimidazole.

d) Aldehyde and ketone derivatives. 4(5)-methylimidazole-5(4)-aldehyde, 4(5)-imidazole aldehyde, and 2-imidazole-phenylketone.

e) Imidazolecarboxylic acids, amides and esters. Among these are 4,5-imidazole-dicarboxylic acid, 2-imidazolecarboxylic acid, 4-imidazolecarboxylic acid, 2-methyl-4(5)-imidazolecarboxylic acid, 4(5)-amino-5(4)-imidazolecarboxamide, 4(5)-amino-5(4)-imidazolecarboxylic acid methyl ester, 2-amino-4,5-imidazole-dicarboxylic acid, and 4-imidazole acetic acid methyl ester.

f) Mercaptoimidazoles. Among these are 2-mercapto-4(5)-imidazolecarboxylic acid methyl ester and ethyl ester.

2. Imidazolines.

Among these are 2-methyl-2-imidazoline, 2-phenyl-2-imidazoline, 2-chloromethyl-2-imidazoline, 2-hydroxymethyl-2-imidazoline, and 2-nitro-2-imidazoline.

3. Imidazolones.

Among these are 2-imidazolone derivatives e.g. 4(5)-methyl-2-imidazolone, 4,5-dimethyl-2-imidazolone, and 2-imidazolone-4-carboxylic acid.

4(5)-imidazolone derivatives e.g. 2-methyl-4(5)-imidazolone, 2-benzyl-4(5)-imidazolone, and 4(5)-imidazolone-2-carboxylic acid.

4. Imidazolidinones (Imidazolidones).

Among these are 2-imidazolidinone (ethylene urea), and imidazolidine-2-thione.

5. Imidazolidines.

Among these is 1,3-dibenzyl-2-phenylimidazolidine.

6. Benzimidazoles.

Among these are alkyl- and aryl-benzimidazoles e.g. 1 - ethylbenzimidazole, 1 - methylbenzimidazole, and 2-benzylbenzimidazole.

hydroxy, nitro, and aminobenzimidazoles e.g. 2 - hydroxymethylbenzimidazole, 5 - nitrobenzimidazole, and 2 - aminobenzimidazole.

benzimidazolecarboxylic acid derivatives e.g. 2 - benzimidazolecarboxylic acid, and 5(6) - methyl - 2 - benzimidazolecarboxylic acid.

Imidazole compounds such as those noted above are generally crystalline. Hence, they are used by dissolving them directly in the polymerization solvent employed for the NCA. Suitable polymerization solvents include dioxane, ethyl acetate, dichloromethane, dichloroethane, dimethylsulfoxide, N-methyl-2-pyrrolidone and N,N-dimethylformamide. Alternatively, the imidazole compounds can be dissolved in a good solvent therefor for example, N,N-dimethylformamide or dimethyl sulfoxide, and the solvent solution of polymerization initiator can then be employed in the polymerization reaction.

The polymerization initiators of the present invention are generally used in an amount of 0.1 mole % or more of the used NCA. No specific restriction is imposed on the manner in which the polymerization initiator is brought into contact with or is mixed with the NCA. A NCA solution or solid NCA may be added to a solution containing an initiator, or the initiator itself, or alternatively a solution containing the initiator or the initiator itself, may be added, as noted above, to a solution or suspension of NCA or to solid NCA.

The solvents used for the polymerization reaction per se include organic ethers, esters, ketones, hydrocarbons, halogenated hydrocarbons, N-substituted aliphatic amides and other organic compounds which will not decompose NCA, for example, dioxane, tetrahydrofuran, ethyl acetate, benzene, toluene, nitrobenzene, dichloromethane, dichloroethane, chloroform, N,N-dimethylformamide, dimethylsulfoxide and N-methyl-2-pyrrolidone. These solvents may be used either singly or in mixtures.

The temperature to be employed during the polymerization reaction is not limited in particular, but usually it is found advantageous to carry out the polymerization at a temperature range of from -20° to 120°C .

The following Examples are given merely as illustrative of the present invention and are not to be considered as limiting. Unless otherwise noted, the percentages therein are by weight.

EXAMPLE 1

Ten g. of the N-carboxy anhydride of L-glutamic acid- γ -methyl ester is dissolved in 100 cc. of dioxane. Then, 115 mg. of N-ethylimidazole is added thereto at room temperature. The polymerization is accomplished in eight hours in a dry nitrogen atmosphere. Methanol is added to the reaction mixture, and the polymer is obtained as a precipitate.

As a result, 7.6 g. (dry weight) of the polymer is obtained. This represents a quantitative yield. The limiting viscosity number (intrinsic viscosity) $[\eta]$ of the product polymer is 1.8, when measured at 25°C . using dichloroacetic acid as the solvent. The same procedure of measurement is also employed in the Examples described hereinbelow.

EXAMPLE 2

Ten g. of the N-carboxy anhydride of L-glutamic acid- γ -methyl ester is added to 120 cc. of a mixed solvent consisting of dioxane and dichloroethane (1:4 by volume ratio). Then, 48 mg. of 2-methylimidazole dissolved in a small amount of dimethylformamide is added to the reaction mixture.

After eight hours of reaction, a highly viscous, clear polymer solution is obtained. After pouring the reaction solution into methanol, a dry polymer (7.55 g. in weight) is obtained. This represents substantially a quantitative yield. The limiting viscosity number $[\eta]$ of the polymer is 1.90, measured as described in Example 1.

EXAMPLE 3

Ten g. of ϵ -N-carbobenzoxyl-L-lysine-N-carboxyanhydride is added to 100 cc. of dioxane, to which 40 mg. of imidazole is added. After 12 hours, a highly viscous solution of poly- ϵ -N-carbobenzoxyl-L-lysine is obtained. The solution is poured into methanol, thereby yielding a polymer having the limiting viscosity number $[\eta]$ of 1.3.

EXAMPLE 4

Ten g. of L-alanine N-carboxy anhydride is dissolved in 100 cc. of dioxane. Added thereto is 75 mg. of N-ethylimidazole. After 12 hours, methanol is added in an amount five times that of the reaction liquid, thereby precipitating the polymer product. The dry weight of poly-L-alanine obtained is 5.9 g. The yield is 95%, and the viscosity number (reduced viscosity) of the polymer is 4.6, when measured in dichloroacetic acid at a concentration of 1% and a temperature of 25°C .

EXAMPLE 5

Ten g. of L-leucine N-carboxy anhydride is dissolved in 100 cc. of ethyl acetate and, after adding 128 mg. of 2-methylimidazole thereto, the polymerization is carried out for 12 hours at room temperature. Then, the

reaction solution is poured into methanol, and the resultant precipitated polymer is separated. The dry weight of the polymer is 6.5 g., representing a yield of 90%. The polymer shows the viscosity number of 3.2.

EXAMPLE 6

Ten g. of γ -methyl-L-glutamic acid N-carboxy anhydride is added to 100 cc. of dichloroethane. 115 mg. of ethylene urea (2-imidazolidinone) dissolved in a small amount of dimethylformamide or dimethyl sulfoxide is added to the reaction solution. After 12 hours, methanol is added, and the precipitated polymer is then separated. The dry weight of the polymer is 7.0 g., representing a yield of 91%, and the limiting viscosity number $[\eta]$ thereof, measured in the same manner as described in Example 1, is 2.8.

EXAMPLE 7

Ten g. of γ -methyl-D,L-glutamic acid N-carboxy anhydride is reacted in the same manner as described in Example 1. As a result, a polymer is obtained having a dry weight of 6.5 g., representing a yield of 85%. The limiting viscosity number $[\eta]$ thereof is 0.8.

WHAT WE CLAIM IS:—

1. A process for the polymerisation of an α -amino acid-N-carboxy anhydride which comprises polymerising said anhydride to give the corresponding poly(amino acid), the polymerisation taking place in the presence of, as polymerisation initiator, imidazole or an aryl-, aralkyl-, alkaryl-, alkyl-, haloalkyl-, halogen-, hydroxyalkyl-, aminoalkyl, nitro-, amino-, mercapto-, aldehydo and/or keto-substituted derivative of imidazole, an imidazolyl carboxylic acid, an imidazolyl carboxylic acid amide, an imidazolyl carboxylic acid alkyl ester, an imidazoline, an imidazolone, an imidazolidinone (imidazo-

lidones), a benzimidazole or imidazolidine or a mixture thereof.

2. The process of claim 1, wherein said polymerisation initiator is used in an amount of at least 0.1 mole % of the said NCA.

3. The process of claim 1 or 2, in which the anhydride is polymerised in an inert organic solvent solution or suspension thereof.

4. The process of any of the preceding claims, wherein the polymerisation reaction is carried out at a temperature of -20° to 120°C .

5. A polymerisable reaction mixture comprising an α -amino acid-N-carboxy anhydride and, as polymerisation initiator, imidazole or an aryl-, aralkyl-, alkaryl-, alkyl-, haloalkyl-, halogen-, hydroxyalkyl-, aminoalkyl, nitro-, amino-, mercapto-, aldehydo-, and/or keto-substituted derivative of imidazole, an imidazolyl carboxylic acid, an imidazolyl carboxylic acid amide, an imidazolyl carboxylic acid alkyl ester, an imidazoline, an imidazolone, an imidazolidinone (imidazolidones), a benzimidazole or imidazolidine or a mixture thereof.

6. The polymerisable reaction mixture of claim 5, wherein said polymerisation initiator is present in an amount of at least 0.1 mole % of the said N-carboxyanhydride.

7. Process of polymerising an α -amino acid-N-carboxy anhydride substantially as described in any of the foregoing Examples.

8. A polymerisable reaction mixture according to claim 5 substantially as described in any of the foregoing Examples.

9. A polymerisation product of the process of any of claims 1 to 4.

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